OSTEOPROTECT: a new therapy of osteoporosis based on sphingosin-1-phosphate and analogues

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8.9 million yearly fractures: 1 every 3 seconds

1 in 3 women over the age of 50 years and 1 in 5 men will experience an osteoporotic fracture in their lifetime

Longer life span and the increasingly aging population have turned osteoporosis into a major burden on public health

More days in a hospital in women over 45 than due to diabetes, cardiovascular disease or breast cancer
Normal balance between bone formation and bone degradation
Osteoporosis: reduced bone formation and increased bone degradation
Current therapy of osteoporosis

• Early diagnosis difficult: no clinical manifestations until a fracture occurs

• Drug therapy consists ONLY of anti-resorptive agents that inhibit bone degradation
  bisphosphonates, estrogen, estrogen receptor modulators, RANKL antibodies

• No drugs that stimulate new bone formation – the ‘holy grail’ in the treatment of osteoporosis
  human parathyroid hormone (Teriparatide®) restricted to special patient groups and a ‘black box’ warning

• Novel osteoanabolic drugs and therapies are dearly sought for
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Ceramide

Sphingosine

S1P

S1P lyase

Ethanolamine phosphate + Hexadecenal

UV radiation
Chemotherapy
Death receptors

Heat stress
UV radiation
Chemotherapy
Death receptors

Growth factors (PDGF, IGF, VEGF)
Cytokines (TNF, IL-1)
oxLDL immune complexes
Hypoxia, Fc receptor

UV radiation
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Growth factors (PDGF, IGF, VEGF)
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immunomodulation (multiple sclerosis, Gilenya®)
angiogenesis and tumor angiogenesis (Sphingomab)
cardiovascular functions

Modified from Hannun and Obeid
Principles of bioactive lipid signalling: lessons from Sphingolipids
NATURE REVIEWS MOLECULAR CELL BIOLOGY 2008
Harayama, NATURE REVIEWS MOLECULAR CELL BIOLOGY 2018
Association between serum S1P and bone health in 4,091 participants of the population-based SHIP-Trend study

Weske, *Nature Medicine* 2018
High S1P levels increase bone mass in mice

Micro-computed tomography

S1P

S1P lyase

ethanolamine phosphate + hexadecenal

4-deoxypyrodoxin (DOP)

Sgpl loxP/loxP β-actCreERT2

Micro-computed tomography

Weske, *Nature Medicine* 2018
High S1P increases bone mineral density and mechanical strength

Corticalis at femoral midshaft

Weske, *Nature Medicine* 2018
High bone FORMATION + Suppressed bone DEGRADATION = more and better bone
Successful therapy of osteoporosis using S1P lyase inhibitors

Osteoporosis due to estrogen deficiency (e.g. after menopause)

Genetic osteoporosis (M. Paget Typ 1)

DOP → S1P

OPG knockout

Weske, Nature Medicine 2018
Successful therapy of osteoporosis using S1P receptor-specific agonists

Osteoporosis due to estrogen deficiency (e.g. after menopause)

[S1P receptor 2]

CYM5520

Weske, *BONE* 2019
Publications


PCT-patent application has been filed (March 2019)

Broad response in the general population TV (WDR), Newspapers (BILD, NZZ), Apothekenrundschau; more than 200 volunteers for clinical studies

Current Pipeline: Successful synthesis of a new and more potent lead substance

Tasks: retrosynthesis and modifications in vitro and preclinical testing biodistribution, pharmacokinetics, toxicity studies, further patenting

Commercial Opportunities: start up, access to rights for commercial use, opportunity for further co-development
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